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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,124	06/08/2001	Edward T.H. Yeh	UTSH:249US	1154

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/878,124	YEH ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *7-13,19-27 and 38-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,14-18 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5&6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-62 are pending.

2. Applicant's election with traverse of Group I, claims 1-6, 14-18, 28-38 and 52, drawn to a method of screening for modulators of C-reactive protein by contacting the at least a first candidate substance comprising assaying for C-reactive protein induction of the expression of an ICAM-1 adhesion molecule filed on 1/21/03, is acknowledged.

Upon reconsideration, Examiner has rejoined Groups I-III, and regard ICAM-1, VCAM and E-selectin as species.

Upon reconsideration, Examiner has extended the search to cover VCAM and E selectin, claims 1-6, 14-18 and 28-37 read on all the species.

Further, a clear and obvious typographical error occurred in the restriction wherein claims 38 and 52 which reads on a method of inhibiting C-reactive protein (CRP) modulated inflammation and a method of screening for a modified modulator respectively were included in Groups I-III which are drawn to a method of screening for modulators of CRP. Claim 38 should belong to Group XIV, while claim 52 should belong to Groups XV-XVII. Therefore claims 38 and 52 are drawn to nonelected inventions.

Applicant's traversal is moot in light of the rejoinder of Groups I-III and the consideration of ICAM-1,VCAM and E-selectin as species.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 7-13, 19-27 and 38-62 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-6, 14-18, 28-37 are under examination as they read on a method of screening for modulators of C-reactive protein by contacting the at least a first candidate substance comprising assaying for C-reactive protein induction of the expression of an ICAM-1, VCAM and E-selectin adhesion molecule.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6, 14-18, 28-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is rejected as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: the resolution step, it unclear how to determine the modulation. No proper controls are setup to compare the inhibition/enhancement of adhesion molecule.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 14-18, 28-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of screening for modulators of human C-reactive protein in serum comprising obtaining a human C-reactive protein from human serum; contacting the C-reactive protein with a candidate substance and assaying for an interaction between the C-reactive protein and the candidate substance by assaying for C-reactive protein induction of the expression of ICAM-1, VCAM or E-selectin in endothelial cells, does not reasonably provide enablement for a method of screening for modulators of any C-reactive protein comprising obtaining a c-reactive protein; contacting the C-reactive protein with the least a first candidate substance, assaying for an interaction between the C-reactive protein and the first candidate substance with any assay that affect the expression of any adhesion molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to identifying modulators of any "C-reactive protein" which effect the expression of any "adhesion molecule".

The specification discloses (page 36, lines 20-24) that the HUVEC cultured in a serum-free medium showed that incubation with 100 μg/ml of C-reactive protein could not induce adhesion molecules expression due to the inability of HUVEC to express adhesion molecules in the

absence of serum. The specification further discloses that the effects of CRP are dependent on the presence of serum. Furthermore, the specification discloses that CRP effects are dependent on one or more serum co-factors (page 36, lines 25-26).

One cannot extrapolate the teachings of the specification to the scope of the claims because the CRP-induced expression of ICAM-1, VCAM and E-selectin by endothelial cells depends on the presence of serum, which involve the one or more serum co-factors. Similarly, Lagrand *et al* (Circulation. 104(9):E46, 2001) indicate that such serum factor(s) remains to be identified, and the role of such complement (serum factor) as an intermediate between CRP and ICAM-1 expression requires that the CRP is able to activate the complement. The claimed method does not have the functional biological properties representative of what is being disclosed in the specification and the literature, and applicant has not enabled any of these methods because it has not been shown that such methods are capable of functioning as that which is being disclosed.

Besides human CRP and ICAM, VCAM and E-selectin, the specification fails to provide any guidance as to how to make and how to use any "C-reactive protein", and any "adhesion molecule".

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation, claim 1 requires any CRP molecule. However, the present specification fails to provide sufficient disclosure of all CRP molecules that maintain the structural and functional properties of the human CRP, wherein the human CRP, in the presence of serum, induce ICAM-1, VCAM and E-selectin in endothelial cells. The specification does not provide sufficient guidance as to which of the amino acids may be changed while CRP functional activity is retained.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that event a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 13006, 2nd column).

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the

nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 1-6, 14-18, 28-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an *in vitro* method of screening for modulators of human C-reactive protein in serum comprising obtaining a human C-reactive protein from human serum; contacting the C-reactive protein with a candidate substance and assaying for an interaction between the C-reactive protein and the candidate substance by assaying for C-reactive protein induction of the expression of ICAM-1, VCAM or E-selectin in endothelial cells.

Applicant is not in possession of any method of screening for modulators of any C-reactive protein comprising obtaining a c-reactive protein; contacting the C-reactive protein with the least a first candidate substance, assaying for an interaction between the C-reactive protein and the first candidate substance with any assay.

Applicant has disclosed only human C-reactive protein; therefore, the skilled artisan cannot envision all the contemplated C-reactive protein possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was

not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 14 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Tseng *et al* (Mol. Immuno. 25:679-686, 1988).

Tseng et al teach a method of screening for modulators of C-reactive protein (CRP) comprising obtaining CRP from human ascites fluids (see abstract and page 680, under Purification of CRP in particular), contacting the CRP with different mAb such as mAbs to CRP that bind at or near the PC-binding site and mAb to the mouse PC-binding idiotype T-15, which also reacts with the PC-binding site of CRP and assaying for an interaction the % inhibition of CRP binding determined on the basis of CRP bound to Fn in the absence of mAb (see Table 2 on page 683 in particular). Tseng *et al* further teach mAb to the mouse PC-binding idiotype T-15 inhibits the binding of CRP to Fn. Tseng *et al* further teach that CRP binds with high affinity to purified plasm fibronectin (Fn) when the Fn is immobilized on a surface or matrix via either specific IgG antibody or by gelatin (see abstract and figure 1 in particular), wherein the binding enhances adhesion.

The reference teachings anticipate the claimed invention.

11. Claims 1, 14, 28 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Cermak *et al* Blood 82:855-860, 1993 (IDS Ref. No. C3).

Cermak *et al* teach a method of screening for modulators of C-reactive protein (CRP) comprising contacting human CRP with tissue factor (TF) and assaying for the production of CRP. Cermak *et al* further teach that TF led to increased production of C-reactive protein. Cermak *et al* further teach that CRP-induced production was completely blocked by a monoclonal antibody against human TF but not by irrelevant murine IgG. Furthermore, Actinomycin D, cycloheximide and anti-human CRP IgG inhibited CRP-induced PCA production blocked CRP-stimulated

production (see abstract, page 513 in particular). Cermak *et al* teach that the incubation times was carried out in RPMI 1640 and 1% FCS.

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 14-18, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tseng *et al* (J Cell. Biochem 50:83-92, 1992) or Cermak *et al* Blood 82:855-860, 1993 (IDS Ref. No. C3), in view of U.S. Patent No. 6,455,046.

The Tseng *et al* and Cermak *et al* references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation that the C-reactive protein is procured by isolation from a cell recited in claim 15, wherein the cell comprises a recombinant nucleic acid sequence encoding a C-reactive protein and C-reactive protein is expressed from the recombinant nucleic acid sequence in claim 16, wherein C-reactive protein is isolated from serum in claim 17, and wherein the serum is human serum in claim 18.

The '046 patent teaches that the native CRP can be obtained from natural sources (e.g., serum, plasma, pleural fluid or ascites fluid). The '046 patent teaches that native CRP can also be produced by recombinant DNA techniques. Genomic and cDNA clones coding for human, mouse, and rabbit CRP have been isolated and sequenced. The '046 patent teaches to obtain native CRP, eukaryotic host cells, preferably mammalian host cells, should be used for the expression of the CRP clone. Finally, the '046 patent teaches that using those isolation methods, CRP can be obtained which is about 99% pure (see column 2, line 67 and column 3, lines 1-48 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the C-reactive protein taught by Tseng et al or Cermak et al from a cell, a recombinant DNA techniques, or human serum as taught by '046 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to to do so because using those isolation methods provides 99% pure CRP as taught by the '046 patent.

Form the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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April 7, 2003

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